



PATENT  
Attorney Docket No.: RIB-005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Steitz *et al.*  
SERIAL NO.: 10/072,634 GROUP NO.: 2683  
FILING DATE: February 8, 2002 EXAMINER: Not yet assigned  
TITLE: Ribosome Structure and Protein Synthesis Inhibitors

Commissioner for Patents  
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with the provisions of 37 C.F.R. 1.97 and 1.98, Applicants hereby make of record the patents and publications listed on the accompanying Form PTO-1449, and other information contained herein, for consideration by the Examiner in connection with the examination of the above-identified patent application. Copies of the patents and publications are enclosed.

REMARKS

In accordance with the provisions of 37 C.F.R. 1.97, this statement is being filed (CHECK ONE):

- ☒ (1) within three (3) months of the **filing date** of a national application other than a continued prosecution application under 37 C.F.R. 1.53(d), or within three (3) months of the **date of entry of the national stage** as set forth in 37 C.F.R. 1.491 in an international application, or before the mailing of the **first Office action** on the merits, or before the mailing of a **first Office action** after the filing of a request for continued examination under 37 C.F.R. 1.114; or
- ☐ (2) after the period defined in (1) but before the mailing date of a **final action** or a **notice of allowance** under 37 C.F.R. 1.311, and
- ☐ the requisite Statement is below, **OR**
- ☐ the requisite fee under 37 C.F.R. 1.17(p), namely **\$180.00**, is included herein, or
- ☐ (3) after the mailing date of a **final action** or **notice of allowance** but before the payment of the **issue fee**, **AND**

- ☐ the requisite Statement is below, **AND**
- ☐ the requisite petition fee under 37 C.F.R. 1.17(p), namely **\$180.00** is included herein.

It is respectfully requested that each of the patents and publications listed on the attached Form PTO-1449, and other information contained herein, be made of record in this application.

### STATEMENT

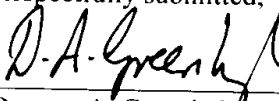
As required under 37 C.F.R. 1.97(e), Applicant(s), through the undersigned, hereby state either that [check the appropriate space only if either (2) or (3) is checked on the previous page and the Statement is required]:

- ☐ 1. Each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application **not more than three months** prior to the filing of the Information Disclosure Statement; or
- ☐ 2. No item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing this Statement after making reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to **any individual** designated in 37 C.F.R. 1.56(c) **more than three months** prior to the filing of the Information Disclosure Statement.

Date: September 26, 2002  
Reg. No.: 38,678

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Respectfully submitted,

  
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## U.S. PATENT DOCUMENTS

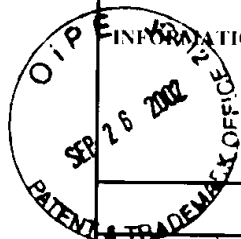
EXAM. INIT.	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

EXAM. INIT.	DOCUMENT NUMBER	DATE	COUNTRY CODE	CLASS	SUB CLASS	FILING DATE	ABSTRACT ONLY	ENGLISH LANG (Y/N)
	B1	EP 1 172 374 A1	01/16/02	EP		07/13/01		Yes
	B2	WO 99/63937 A3	12/16/99	PCT		06/08/99		Yes
	B3	WO 01/80863 A1	11/01/01	PCT		04/27/01		Yes

## OTHER ART, JOURNAL ARTICLES, ETC.

EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)	
	C1	Agalarov, S., <i>et al.</i> , (2000) "Structure of the S15, S6, S18-rRNA Complex: Assembly of the 30S Ribosome Central Domain," <u>Science</u> Vol. 288, pp. 107-112
	C2	Agrawal, R., <i>et al.</i> , (1998) "Visualization of Elongation Factor G on the <i>Escherichia coli</i> 70S Ribosome: The Mechanism of Translocation," <u>Proc. Natl. Acad. Sci. USA</u> Vol. 95, pp. 6134-6138
	C3	Ban, N., <i>et al.</i> , (2000) "The Complete Atomic Structure of the Large Ribosomal Subunit at 2.4 Å Resolution," <u>Science</u> Vol. 289, No. 5481, pp. 821-1096
	C4	Ban, N., <i>et al.</i> , (1999) "Placement of Protein and RNA Structures into a 5 Å-Resolution Map of the 50S Ribosomal Subunit," <u>Nature</u> Vol. 400, pp. 841-847
	C5	Ban, N., <i>et al.</i> , (1998) "A 9 Å Resolution X-Ray Crystallographic Map of the Large Ribosomal Subunit," <u>Cell</u> Vol. 93, pp. 1105-1115
	C6	Baranov, P., <i>et al.</i> , (1998) "The Database of Ribosomal Cross Links (DRC)," <u>Nucleic Acids Research</u> Vol. 26, No. 1, pp. 187-189
	C7	Brodersen, D., <i>et al.</i> , (2000) "The Structural Basis for the Action of the Antibiotics Tetracycline, Pactamycin, and Hygromycin B on the 30S Ribosomal Subunit," <u>Cell</u> Vol. 103, pp. 1143-1154
	C8	Brünger, A., <i>et al.</i> , (1998) "Crystallography & NMR System: A New Software Suite for Macromolecular Structure Determination," <u>Acta Cryst.</u> Vol. D54, pp. 905-921
	C9	Brünger, A., (1997) "Patterson Correlation Searches and Refinement," <u>Methods in Enzymology</u> , Vol. 276, pp. 558-580
	C10	Carter, A., <i>et al.</i> , (2001) "Crystal Structure of an Initiation Factor Bound to the 30S Ribosomal Subunit," <u>Science</u> Vol. 291, pp. 498-501



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## OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)

C11	Carter, A., <i>et al.</i> , (2000) "Functional Insights from the Structure of the 30S Ribosomal Subunit and It's Interactions with Antibiotics," <u>Nature</u> Vol. 407, pp. 340-348
C12	Cate, J., <i>et al.</i> , (1999) "X-Ray Crystal Structures of 70S Ribosome Functional Complexes," <u>Science</u> Vol. 285, No. 5, pp. 2095-2104
C13	Clemons, W. Jr., <i>et al.</i> , (1999) "Structure of a Bacterial 30S Ribosomal Subunit at 5.5 Å Resolution," <u>Nature</u> Vol. 400, pp. 833-840
C14	Culver, G., <i>et al.</i> , (1999) "Identification of an RNA-Protein Bridge Spanning the Ribosomal Subunit Interface," <u>Science</u> Vol. 285, pp. 2133-2135
C15	Dahlberg, A., <i>et al.</i> , (2001) "The Ribosome in Action," <u>Science</u> Vol. 292, pp. 868-869
C16	Davies, C., <i>et al.</i> , (1998) "Ribosomal Proteins S5 and L6: High-Resolution Crystal Structures and Roles in Protein Synthesis and Antibiotic Resistance," <u>Journal of Molecular Biology</u> , Vol. 279, pp. 873-888
C17	Di Giambattista, M., <i>et al.</i> , (1990) "Affinity Labeling of the Virginiamycin S <sub>1</sub> Binding Site on Bacterial Ribosome," <u>Biochemistry</u> Vol. 29, pp. 9203-9211
C18	Douthwaite, S., <i>et al.</i> , (1995) "Recognition Determinants for Proteins and Antibiotics within 23S rRNA," <u>Biochem. Cell Biol.</u> Vol. 73, pp. 1179-1185
C19	Douthwaite, S., <i>et al.</i> , (1993) "Erythromycin Binding is Reduced in Ribosomes with Conformational Alterations in the 23 S rRNA Peptidyl Transferase Loop," <u>Journal Mol. Biol.</u> Vol. 232, pp. 725-731
C20	Douthwaite, (1992) "Functional Interactions within 23S rRNA Involving the Peptidyltransferase Center," <u>Journal of Bacteriology</u> Vol. 174, No. 4, pp. 1333-1338
C21	Fitzhugh, A., <i>et al.</i> , (1998) "Antibiotic Inhibitors of the Peptidyl Transferase Center. 1. Clindamycin as a Composite Analogue of the Transfer RNA Fragments L-Pro-Met and the D-Ribosyl Ring of Adenosine," <u>Bioorganic and Medicinal Chemistry Letters</u> , Vol. 8, pp. 87-92
C22	Gabashvili, I., <i>et al.</i> , (2000) "Solution Structure of the <i>E. coli</i> 70S Ribosome at 11.5 Å Resolution," <u>Cell</u> , Vol. 100, pp. 537-549
C23	Garrett, R., <i>et al.</i> , (1996) "The Peptidyl Transferase Center," <u>Ribosomal RNA</u> pp. 327-355
C24	Garza-Ramos, G., <i>et al.</i> , (2001) "Binding Site of Macrolide Antibiotics on the Ribosome: New Resistance Mutation Identifies a Specific Interaction of Ketolides with rRNA," <u>Journal of Bacteriology</u> , Vol. 183, No. 23, pp. 6898-6907
C25	Gonzales, R., <i>et al.</i> , (2001) "Infections Due to Vancomycin-Resistant <i>Enterococcus faecium</i> Resistant to linezolid," <u>The Lancet</u> Vol. 357, p. 1179
C26	Green, R., <i>et al.</i> , (1997) "Ribosomes and Translation," <u>Annu. Rev. Biochemistry</u> Vol. 66, pp. 679-716



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EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)	
	C27	Gregory, S., <i>et al.</i> , (1999) "Erythromycin Resistance Mutations in Ribosomal Proteins L22 and L4 Perturb the Higher Order Structure of 23 S Ribosomal RNA," <u>J. Mol. Biol.</u> Vol. 289, pp. 827-834
	C28	Gschwend, D. <i>et al.</i> , (1996) "Molecular Docking Towards Drug Discovery," <u>Journal of Molecular Recognition</u> , Vol. 9, pp. 175-186
	C29	Guettell, R. (1996) "Comparative Sequence Analysis and the Structure of 16S and 23S rRNA," <u>Ribosomal RNA</u> pp. 111-128
	C30	Hansen, H.A.S., <i>et al.</i> , (1990) "Crystals of Complexes Mimicking Protein Biosynthesis are Suitable for Crystallographic Studies," <u>Biochimica et Biophysica Acta</u> , Vol. 1050, pp. 1-7
	C31	Harms, J., <i>et al.</i> , (2001) "High Resolution Structure of the Large Ribosomal Subunit from a Mesophilic Eubacterium," <u>Cell</u> , Vol. 107, pp. 679-688
	C32	Harms, J., <i>et al.</i> , (1999) "Elucidating the Medium-Resolution Structure of Ribosomal Particles: an Interplay between Electron Cryo-Microscopy and X-ray Crystallography," <u>Structure</u> Vol. 7, No. 8, pp. 931-941
	C33	Hansen, L., <i>et al.</i> , (1999) "The Macrolide-Ketolide Antibiotic Binding Site is Formed by Structures in Domains II and V of 23S Ribosomal RNA," <u>Molecular Microbiology</u> , Vol. 31, No. 2, pp. 623-631
	C34	Kloss, P., <i>et al.</i> , (1999) "Resistance Mutations in 23 S rRNA Identify the Site of Action of the Protein Synthesis Inhibitor Linezolid in the Ribosomal Peptidyl Transferase Center," <u>J. Mol. Biol.</u> Vol. 294, No. 1, pp. 93-101
	C35	Lázaro, E., <i>et al.</i> , (1996) "A Sparsomycin-Resistant Mutant of <i>Halobacterium salinarum</i> Lacks a Modification at Nucleotide U2603 in the Peptidyl Transferase Centre of 23 S rRNA," <u>J. Mol. Biol.</u> Vol. 261, No. 2, pp. 231-238
	C36	Lázaro, E., <i>et al.</i> , (1991) "Chemical, Biochemical and Genetic Endeavors Characterizing the Interaction of Sparsomycin with the Ribosome," <u>Biochimie</u> Vol. 73, pp. 1137-1143
	C37	Lipinski, C., <i>et al.</i> , (1997) "Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings," <u>Adv. Drug Delivery Rev.</u> Vol. 23, No. 3-25
	C38	Maskowski <i>et al.</i> , (1987) "Single Crystals of Large Ribosomal Particles from <i>Halobacterium marismortui</i> Diffract to 6 Å," <u>Journal Molecular Biology</u> Vol. 193 pp. 818-822
	C39	Matadeen, R., <i>et al.</i> , (1999) "The <i>Escherichia Coli</i> Large Ribosomal Subunit at 7.5 Å Resolution," <u>Structure</u> , Vol. 7, No. 12, pp. 1575-1583
	C40	Moazed <i>et al.</i> , (1989) "Interaction of +RNA with 23S rRNA in the Ribosomal A, P, and E Sites," <u>Cell</u> Vol. 57, pp. 585-597
	C41	Moazed, D., <i>et al.</i> , (1987) "Chloramphenicol, Erythromycin, Carbomycin and Vernamycin B Protect Overlapping Sites in the Peptidyl Transferase Region of 23S Ribosomal RNA," <u>Biochimie</u> Vol. 69, pp. 879-884

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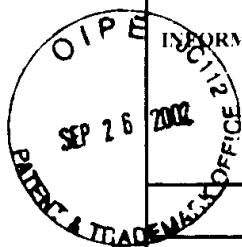
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| C42 | Moore, P.B. (1999) "Structural Motifs in RNA," <u>Ann. Rev. Biochemistry</u> Vol. 67, pp. 287-300   |
| C43 | Moore, P.B. (1998) "The Three-Dimensional Structure of the Ribosome and its Components," <u>Ann. Rev. Biophys.</u> Vol. 27, pp. 35-58   |
| C44 | Mueller, F., <i>et al.</i> , (2000) "The 3D Arrangement of the 23 S and 5 S rRNA in the <i>Escherichia coli</i> 50 S Ribosomal Subunit Based on a Cryo-Electron Microscopic Reconstruction at 7.5 Å Resolution," <u>J. Mol. Biol.</u> Vol. 298, pp. 35-59 |
| C45 | Mussig, J., <i>et al.</i> , (1989) "Crystals of Wild-type, Mutated, Derivatized and Complexed 50 S Ribosomal Subunits from <i>Bacillus stearothermophilus</i> Suitable for X-ray Analysis," <u>J. Mol. Biol.</u> Vol. 205, pp. 619-621                    |
| C46 | Nakatogawa, H., <i>et al.</i> , (2002) "The Ribosomal Exit Tunnel Functions as a Discriminating Gate," <u>Cell</u> Vol. 108, pp. 629-636  |
| C47 | Navaza, J., <i>et al.</i> , (1997) "AMoRe: An Automated Molecular Replacement Program Package," <u>Methods in Enzymology</u> Vol. 276, pp. 581-595  |
| C48 | Nissen, P., <i>et al.</i> , (2000) "The Structural Basis of Ribosome Activity in Peptide Bond Synthesis," <u>Science</u> Vol. 289, pp. 920-930  |
| C49 | Nitta, I., <i>et al.</i> , (1998) "Reconstitution of Peptide Bond Formation with <i>Escherichia coli</i> 23S Ribosomal RNA Domains," <u>Science</u> Vol. 281, pp. 666-669   |
| C50 | Noller, H., (1991) "Ribosomal RNA and Translation," <u>Ann. Rev. Biochemistry</u> Vol. 60, pp. 191-227  |
| C51 | Ogle, J., <i>et al.</i> , (2001) "Recognition of Cognate Transfer RNA by the 30S Ribosomal Subunit," <u>Science</u> Vol. 292, pp. 897-902   |
| C52 | Pestka, S., (1974) "Antibiotics as Probes of Ribosome Structure: Binding of Chloramphenicol and Erythromycin to Polyribosomes; Effect of Other Antibiotics," <u>Antimicrobial Agents and Chemotherapy</u> Vol. 5, No. 3, pp. 255-267                      |
| C53 | Porse, B., <i>et al.</i> , (1999) "Ribosomal Mechanics, Antibiotics, and GTP Hydrolysis," <u>Cell</u> Vol. 97, pp. 423-426  |
| C54 | Porse, B., <i>et al.</i> , (1999) "Sites of Interaction of Streptogramin A and B Antibiotics in the Peptidyl Transferase Loop of 23 S rRNA and the Synergism of Their Inhibitory Mechanisms," <u>J. Mol. Biol.</u> Vol 286, No. 2, pp. 375-387            |
| C55 | Ramakrishnan, V., (2002) "Ribosome Structure and the Mechanism of Translation," <u>Cell</u> Vol. 108, pp. 557-572   |
| C56 | Ramakrishnan, V., <i>et al.</i> , (1995) "Structures of Prokaryotic Ribosomal Proteins: Implications for RNA Binding and Evolution," <u>Biochem. Cell Biol.</u> Vol. 73, pp. 979-986  |



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EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)	
	C57	Rodriguez-Fonseca, C., <i>et al.</i> , (1995) "Fine Structure of the Peptidyl Transferase Centre on 23 S-like rRNAs Deduced from Chemical Probing of Antibiotic-Ribosome Complexes," <u>J. Mol. Biol.</u> Vol. 247, pp. 224-235
	C58	Schlünzen, F., <i>et al.</i> , (2001) "Structural Basis for the Interaction of Antibiotics with the Peptidyl Transferase Centre in Eubacteria," <u>Nature</u> Vol. 413, pp. 814-821
	C59	Schlünzen, F., <i>et al.</i> , (2000) "Structure of Functionally Activated Small Ribosomal Subunit at 3.3 Å Resolution," <u>Cell</u> Vol. 102, pp. 615-623
	C60	Schlünzen, F., <i>et al.</i> , (1995) "A Milestone in Ribosomal Crystallography: The Construction of Preliminary Electron Density Maps at Intermediate Resolution," <u>Biochemistry Cell Biology</u> Vol. 73, pp. 739-749
	C61	Shinabarger, D., <i>et al.</i> , (1997) "Mechanism of Action of Oxazolidinones: Effects of Linezolid and Eperezolid on Translation Reactions," <u>Antimicrobial Agents and Chemotherapy</u> Vol. 41, No. 10, pp. 2132-2136
	C62	Spahn, C.M.T., <i>et al.</i> , "Throwing a Spanner in the Works: Antibiotics and the Translation Apparatus," <u>Journal of Molecular Medicine</u> , Vol. 74, No. 8, pp. 423-439
	C63	Swaney, S., <i>et al.</i> , (1998) "The Oxazolidinone Linezolid Inhibits Initiation of Protein Synthesis in Bacteria," <u>Antimicrobial Agents and Chemotherapy</u> Vol. 42, No. 12, pp. 3251-3255
	C64	Tenson, T., <i>et al.</i> , (2002) "Regulatory Nascent Peptides in the Ribosomal Tunnel," <u>Cell</u> Vol. 108, pp. 591-594
	C65	Timmermans, P., <i>et al.</i> , (1982) "Sparsophenicol: A New Synthetic Hybrid Antibiotic Inhibiting Ribosomal Peptide Synthesis" <u>J. Med. Chem.</u> Vol. 25, pp. 1123-1125
	C66	Tocij, A., <i>et al.</i> , (1999) "The Small Ribosomal Subunit from <i>Thermus Thermophilus</i> at 4.5 Å Resolution: Pattern Fittings and the Identification of a Functional Site," <u>Proc. Natl. Acad. Sci. USA</u> Vol. 96, pp. 14252-14257
	C67	Trakhanov, S.D., <i>et al.</i> , (1987) "Crystallization of 70 S Ribosomes and 30 S Ribosomal Subunits from <i>Thermus thermophilus</i> ," <u>Febs Letters</u> , Vol. 220, No. 2, pp. 319-322
	C68	Tronrud, D., (1997) "TNT Refinement Package," <u>Macromolecular Crystallography, Part B, Methods in Enzymology</u> Vol. 277, pp. 306-319
	C69	Tsiodras, S., <i>et al.</i> , (2001) "Linezolid Resistance in a Clinical Isolate of <i>Staphylococcus Aureus</i> ," <u>The Lancet</u> Vol. 358, pp. 207-208
	C70	Vannuffel <i>et al.</i> , (1996) "Mechanism of Action of Streptogramins and Macrolides," <u>Drugs</u> Vol. 51, Suppl 1, pp. 20-30
	C71	Vannuffel <i>et al.</i> , (1992) "Identification of a Single Base Change in Ribosomal RNA Leading to Erythromycin Resistance," <u>J. Biol. Chem.</u> Vol. 267(12), pp. 8377-8382



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## OTHER ART, JOURNAL ARTICLES, ETC

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C72	Vester <i>et al.</i> , (2001) "Macrolide Resistance Conferred by Base Substitutions," <u>Antimicrobial Agents and Chemotherapy</u> Vol. 45, No. 1, pp. 1-12
C73	Vester <i>et al.</i> , (1988) "The Importance of Highly Conserved Nucleotides in the Binding Region of Chloramphenicol at the Peptidyl transfer Centre of <i>Escherichia coli</i> 23S Ribosomal RNA," <u>The EMBO Journal</u> Vol. 7, No. 11, pp. 3577-3587
C74	Volkman <i>et al.</i> , (1990) "Characterization and Preliminary Crystallographic Studies on Large Ribosomal Subunits from <i>Thermus thermophilus</i> ," <u>J. Mol. Biol.</u> Vol. 216, pp. 239-241
C75	Von Bohlen (1991) "Characterization and Preliminary Attempts for Derivatization of Crystals of Large Ribosomal Subunits from <i>Haloarcula marismortui</i> Diffracting to 3 Å Resolution," <u>J. Mol. Biol.</u> Vol. 222, pp. 11-15
C76	Welch, M., <i>et al.</i> , (1997) "23S rRNA Similarity from Selection for Peptidyl Transferase Mimicry," <u>Biochemistry</u> Vol. 36, pp. 6614-6623
C77	Welch, M., <i>et al.</i> , (1995) "An Inhibitor of Ribosomal Peptidyl Transferase Using Transition-State Analogy," <u>Biochemistry</u> Vol. 34, pp. 385-390
C78	Wimberly, B., <i>et al.</i> , (2000) "Structure of the 30S Ribosomal Subunit," <u>Nature</u> Vol. 407, pp. 327-339
C79	Wittmann <i>et al.</i> , (1982) "Crystallization of <i>Escherichia coli</i> Ribosomes," <u>Febs Letters</u> Vol. 146, No. 1, pp. 217-220
C80	Wool, L., <i>et al.</i> , (1995) "Structure and Evolution of Mammalian Ribosomal Proteins," <u>Biochemistry Cell Biology</u> Vol. 73, pp. 933-947
C81	Xiong, L., <i>et al.</i> , (2000) "Oxazolidinone Resistance Mutations in 23S rRNA of <i>Escherichia coli</i> Reveal the Central Region of Domain V as the Primary Site of Drug Action," <u>Journal of Bacteriology</u> Vol. 182, No. 19, pp. 5325-5331
C82	Yonath, A., <i>et al.</i> , (1998) "Crystallographic Studies on the Ribosome, a Large Macromolecular Assembly Exhibiting Severe Nonisomorphism, Extreme Beam Sensitivity and No Internal Symmetry," <u>Acta Cryst.</u> Vol. A54, pp. 945-955
C83	Yonath, A., <i>et al.</i> , (1986) "Characterization of Single Crystals of the Large Ribosomal Particles from <i>Bacillus stearothermophilus</i> ," <u>J. Mol. Biol.</u> Vol. 187, pp. 633-636
C84	Yusupov, G., <i>et al.</i> , (2001) "The Path of Messenger RNA through the Ribosome," <u>Cell</u> Vol. 106, pp. 233-241
C85	Yusupov, M., <i>et al.</i> , (2001) "Crystal Structure of the Ribosome 5.5 Å Resolution," <u>Science</u> Vol. 292, pp. 883-896
C86	Yusupov, M., <i>et al.</i> , (1991) " <i>Thermus thermophilus</i> Ribosomes for Crystallographic Studies," <u>Biochimie</u> Vol. 73, pp. 887-897
C87	Zemlicka, J., <i>et al.</i> , (1993) "Hybrids of Antibiotics Inhibiting Protein Synthesis. Synthesis and Biological Activity," <u>J. Med. Chem.</u> Vol. 36, pp. 1239-1244
C88	European Search Report for Application No. 01306825.9 dated May 24, 2002